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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

ATTACHMENT TO ADVISORY ACTION

11. CONT. Applicant's arguments have been respectfully reconsidered but have not been found persuasive.

1. Status of claims. Claims 1-20, 22-43 are currently pending. Claims 9, 18, and 29 were previously withdrawn from further consideration pursuant to 37 CFR1.14(b) as being drawn to nonelected species.
2. Therefore, claims 1-8, 10-17, 19, 20, 22-28 and 30-43 are currently under examination to which the following grounds of rejection are applicable
3. Please, note that the claim listing provided and filed on 03-10-2009 has not been entered. Accordingly, Applicants' arguments are only addressed to the extent that they don't rely upon the proposed amendments.

Response to arguments

Rejections/Objections withdrawn in response to Applicant arguments or amendments:

Claim Rejections - 35 USC § 103

Claims 1-3, 6-8, 10-12, 15-17, 19, 22-23, 26-28, 30-43 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Peleg et al., (WO 03/004599 A2, Date of Publication 16-Jan-2003) in view or Matsuda et al. (J. of Bacteriology, 1985, p. 1222-1228) or Ishii et al., (Journal of Fermentation and Bioengineering , 1994, pp. 591-597) or Kim et al., (Biotechnology Letters, 2001, pp. 1067-1071).

Reply to applicant arguments as they relate to rejection of claims 1-3, 6-8, 10-12, 15-17, 19, 22-23, 26-28, 30-43 under 35 USC § 103

At pages 10-16 of Remarks filed on 03-10-2008, Applicants essentially assert that there is not suggestion or motivation to combine the teachings of Peleg et al., with Matsuda et al. Ishii et al., or Kim et al.,. Specifically, Applicants content that Peleg deals with making a fusion polypeptide comprising a viral-derived TAT signal peptide and the combined disclosure of Matsuda, Ishii and Kim merely mention the gac gene signal sequence. Therefore, Applicants allege that there is not teaching or suggestion in "this group of references to make Applicants' invention employing a fusion protein that includes a signal sequence of the gac gene of P. *diminuta,* and in some claimed embodiments, the promoter and/or ribosomal binding site of the same gac gene, and a polypeptide of interest other than the gac gene of *P. diminuta*, all linked in such a way in the fusion protein so as to cause the latter to be released into the periplasm of the host cell upon expression of the polynucleotide in the host cell". Moreover, Applicants contend that no support is provided by the Examiner's statement related to a number of bacterial signal peptides for transport of proteins from the cytoplasm to the periplasmic space known in the art. Thus any researcher reading Peleg would likely select virally derived TAT signal peptide as options leading to expected success. In other words, there is not reason for a person of ordinary skill in the art to seek out references related to gac signal sequences of *P. diminuta* based on Peleg alone. In addition, Applicants argue the "insurmountable degree of unpredictably when components from across domains of life are intermingled in a single expression system ". Accordingly, Applicants assert that the Examiner' reasons for obviousness wherein every new

combination of signal peptide and protein may be try in any expression system is essentially faulty. Such is not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As stated in the office action filed on 12-12-2007, Peleg clearly discloses "that transport of proteins through the inner membrane to the periplasmic space requires the inclusion of a signal peptide" (p. 3, lines 8-10). Peleg described a "signal sequence" as a "short (e.g., 15-40) amino acid sequences, which allows proteins to transport through the bacterial inner membrane of he periplasm" (p. 21, lines 23-26) and discloses the structure and functionality of bacterial signal peptides well known in the art from mycoplasmas, other gram positive bacteria and *E. coli* (p. 26, lines 27-30 bridging to p. 27, lines 1-19). Host cells suitable for use with Peleg's expression system include *Pseudomonas* (page 12, line 29). The combined disclosure of Matsuda, Kim and Ishii complement the teachings of Peleg by disclosing a signal sequence of the gac gene of *Pseudomonas diminuta*. Note that the nucleotide sequence GL 7-ACA acylase gene taught by Matsuda et al. comprises SEQ ID No. 2 , i.e., signal peptide, and SEQ ID NO. 5, i.e., promoter region and ribosomal biding site as set forth and claimed in the instant invention. As the signal sequence of the gac gene of glutaryl (GL) 7-ACA acylase gene from *Pseudomonas sp.* GK16 was useful for translocation of the GL 7-ACA acylase into the periplasm in *E. coli (*see Matsuda disclosure, for example) one of ordinary skill in the art should reasonably expect the signal sequence of the gac gene of *Pseudomona* to release the heterologous fusion protein of interest into the periplasm of

the host cell in the fusion protein taught by Peleg for the same reason it secretes GL 7-ACA acylase into the periplasm in *E. coli* . Applicants have provided no evidence to the contrary. Applicants' arguments of unpredictably because of numerous signal peptides are known across all domains of life that will obviate the instant invention (page 12, last paragraph) are not to the point. Specific signal peptides of bacterial or viral origin are disclosed as functional cognates in the teachings of Peleg to be used in Peleg's recombinant fusion system for production of heterologous proteins.

Claims 4, 5, 13, 14, 24 and 25 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Peleg et al., (WO 03/004599 A2, Date of Publication 16-Jan-2003) in view of Matsuda et al. (J. of Bacteriology, 1985, p. 1222-1228), Ishii et al., (Journal of Fermentation and Bioengineering , 1994, pp. 591-597), Kim et al., (Biotechnology Letters, 2001, pp. 1067-1071) as applied to claims 1-3, 6-8, 10-12, 15-17, 19, 22-23, 26-28, 30-43 above, and further in view of Kwon et al., WO 01/057217, (Date of publication 9 August 2001).

Reply to applicant arguments as they relate to rejection of claims 4, 5, 13, 14, 24 and 25 under 35 USC § 103

At page 17 of Remarks, Applicants essentially argue that no indication is given in Kwon that any signal sequence not native to *E. coli* (such as the *P. diminuta*-derived signal sequence of the present claims) would be of any use in an expression system for producing a polypeptide of interest according to Applicants' claims. Thus the mere fact that Kwon discloses hIFNαt-2a and hIFNα-2b as a polypeptide of interest in one expression system says nothing about the

performance of those proteins in other expression systems, or makes any suggestion as to what, if any, alternative expression system might be suitable. Such is not persuasive.

The examiner is relying on Kwon for the specific type of polypeptide being released into the periplasm of the host cell. The polypeptide released into the periplasm of the host cell after the signal sequence is cleaved off the fusion protein is irrelevant to the type of heterologous protein but pertinent to the fusion protein comprising a signal peptide. . Thus a construct comprising inclusion of a signal peptide into the fusion protein would reasonably be expected to release a mature protein into the periplasm of the host cell, absent evidence to the contrary. Accordingly, the interferon alpha 2 of Kwon would had been released into the periplasmic space when expressed in the expression vector generated by the combined disclosure of Peleg et al., Matsuda et al. Ishii et al., and Kim et al., for the same reason it is released from the fusion protein encoded by the vector of Kwon.

Objection

Claim 10 remains objected for the reasons of record as set forth in the action of 12-10-2008. Applicants' arguments rely upon and are directed to the proposed amendments. As the claims' amendment has not been entered, applicants' arguments based on the proposed amendment are not persuasive. Therefore, the rejections of record are maintained.

Claim Rejections - 35 USC § 112- Second Paragraph

Claims 16, 27, 42 and 43 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language. Applicants' arguments rely upon and are directed to the proposed amendments. As the claims' amendment has not been entered, applicants' arguments based on the proposed amendment are

not persuasive. Therefore, the rejections of record as set forth in the action of 12-10-2008 are maintained.

Claim Rejections - 35 USC § 112- First paragraph- New Matter

Claim 43 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Applicants' arguments rely upon and are directed to the proposed amendments. As the claims' amendment has not been entered, applicants' arguments based on the proposed amendment are not persuasive. Therefore, the rejections of record as set forth in the action of 12-10-2008 are maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Maria Leavitt/

Maria Leavitt, PhD
Examiner, Art Unit 1633